

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X15735	FOR FURTHER ACTION		See Form PCT/PEAA16
International application No. PCT/US2004/013004	International filing date (day/month/year) 11.05.2004	Priority date (day/month/year) 11.06.2003	
International Patent Classification (IPC) or national classification and IPC C07D207/14, C07D409/12, C07D405/12, C07D401/12, A61K31/4025, A61P25/00			
Applicant ELI LILLY AND COMPANY et al.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 7 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input checked="" type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application			
Date of submission of the demand 15.03.2005		Date of completion of this report 30.06.2005	
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>		Authorized Officer Telephone No. +49 89 2399- 7818 Schumacher, J.	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**International application No.
PCT/US2004/013004**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-139 as originally filed

Claims, Numbers

1-36 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/013004

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27-32,34-36

because:

☒ the said international application, or the said claims Nos. 27-32 and 34-36 for industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2004/013004

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	6-36
	No: Claims	1-5
Inventive step (IS)	Yes: Claims	
	No: Claims	1-36
Industrial applicability (IA)	Yes: Claims	1-26,33
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 27-32 and 34-36 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 The following documents are referred to in this communication:
D1 : EP 1 125 922 A1 (WELFIDE CORP. OSAKA-SHI, JAPAN) 22 August 2001
D2 : WO 01/66521 A (ACADIA PHARMA., INC, US) 13 September 2001
D3 : THOMAS RYCKMANS ET AL, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 12, no. 2, 2002, pages 261-264, XP002974382
D4 : STERNFELD F ET AL, JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. vol. 42, no. 4, 25 February 1999, pages 677-690, XP002149743
D5: WO 03/024928 A (BOEHRINGER INGELHEIM INT ; NOVO NORDISK AS (DK)) 27 March 2003

2 NOVELTY, ARTICLE 33(1) AND 33(2) PCT:

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 1-5 is not novel in the sense of Article 33(2)PCT.

The specific compound 14a on scheme 2 p.679 of D4 falls within the scope of current claims 1-5. (the definition of R¹ and R² being respectively α -methylbenzyl and methyl in the preparation thereof disclosed on p.687).

Thus, D4 anticipates the subject-matter of present claims 1-5 and the requirements for novelty are not considered to be met.

The compounds of D1 differ from the claimed compounds mainly on account of the substitution ever present on the nitrogen of the pyrrolidine ring.

The amino substituent on the compounds of D2 and D5 is always acylated.

The compounds of D3 have a piperidine ring instead of the pyrrolidine ring.

3. INVENTIVE STEP, ARTICLE 33(3) PCT:

The current application is related to 4-disubstituted amino-pyrrolidines as inhibitors of monoamine reuptake like, serotonin, noradrenaline or dopamine. These compounds are therefore useful in the treatment of central and/or peripheral nervous system disorders.

D2 is considered to be the closest prior art since it discloses 4-disubstituted amino-pyrrolidines as serotonin reuptake inhibitors (see claim 8, p.133, l.23-26). These compounds differ from those claimed because the 4-amino substituent is always acylated. The problem to be solved by the present invention may therefore be regarded as the provision of further inhibitors of monoamine reuptake.

In view of D3, the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

It is common technical knowledge to consider that a -CO- linker is equivalent (isostere) of a -CH₂- linker. Furthermore, from compounds 12 and 13 of D3, which are both shown to be serotonin reuptake inhibitors, it is clear that the skilled person would be lead to replace the acyl group by an methylene group and leave the nitrogen of the pyrrolidine ring without substituent (which is also suggested by claim 1 of D2, since R can be hydrogen).

Therefore the features disclosed in D3 and D2 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed.

Accordingly, the technical problem underlying the present application has to be seen in the provision of 4-disubstituted pyrrolidines which have an unexpected advantageous effect with regard to the serotonin reuptake inhibitors of D2.

However, the description does neither contain any evidence for the alleged activity (on p.133-139, there are only methods to describe how the tests are performed but no evidence that these molecules are indeed active), nor any evidence for a surprising effect with regard to the compounds of D2.

In the absence of evidence for such unexpected effect compared to D2, an inventive step cannot be acknowledged and Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY:

**INTERNATIONAL PRELIMINARY
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(SEPARATE SHEET)**

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For the assessment of the present claims 27-32 and 24-36 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004/000808	31.12.2003	20.06.2003	24.06.2003
WO2004/030668	15.04.2004	30.09.2003	04.10.2002
WO2004/052858	24.06.2004	25.11.2003	06.12.2002

These documents are related to 4-disubstituted amino-piperidines as reuptake inhibitors.